HYPOTHESIS 1: NCS EARLY ORIGINS OF ADULT HEALTH WORKING GROUP
Hypotheses Submitted to Study Design Working Group

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Introduction

The EOAH Working Group has spent considerable time discussing how best to put forward hypotheses that could foster optimal study design of the NCS. The consensus was that instead of submitting a number of hypotheses individually, we should enumerate the principles that underlie all of the hypotheses, then give illustrative examples. Thus this submission differs somewhat from others; its format is as follows:

- Purpose of EOAH Working Group
- Approach to hypothesis generation
- General principles of the field of EOAH that underlie proposed NCS hypotheses
- Target outcomes (adult health states worth studying)
- Illustrative hypotheses
  - Some more developed than others
  - Single spreadsheet proposing measurement domains across all hypotheses

Purpose

The aims of the Early Markers for Adult Disease Working Group are

- to assert that intergenerational, fetal, and childhood factors affect the development of adult chronic disease;
- to formulate specific hypotheses that arise from this thesis;
- to ensure that the design of the NCS incorporates measures that will allow analysis of these and related hypotheses;
- to lead or assist in conducting the analyses

Hypothesis Generation

Overall Approach

- Enumerate general principles (below)
- Identify serious and prevalent adult diseases that may have early origins and that can be measured by intermediate markers within the first 20 years of life
- Identify those intermediate markers
- Identify exposure domains
- Identify hypotheses that
  - Meet the principles
  - Have appropriate intermediate markers
  - Address exposures of interest
  - Meet additional criteria for a useful hypotheses, chiefly adequate exposure and outcome prevalence such that the sample size is adequate

General Principles

The working group developed a list of principles that should govern hypothesis formation regarding research on early origins of adult health. These statements embrace both theoretical and pragmatic issues. Since this field is relatively new and perhaps not so familiar to the entire NCS research community, the Working Group felt it important to enumerate them.

The overarching principles are that susceptibility to adult chronic disease is determined by a dynamic process that occurs over the lifespan. Perturbations ("insults") that determine adult health states may occur anywhere from pre-conception to embryonic, fetal, infant, childhood, adolescent (and adult) life. These insults can affect both somatic growth and maturation of metabolic systems, and they include a range of determinants, including societal, lifestyle, and biological. These determinants act in concert with each other.

The "lifecourse approach to chronic disease" is what some have dubbed the scientific approach that arises from these principles. We find this term useful, as it reminds us to formulate our hypotheses from these principles and to recommend overall study design features to the NCS. This approach allows determinants to work in several different ways. One classification scheme groups conceptual models under 4 headings (Ben-Shlomo and Kuh 1999):

- A critical period model, in which an insult during a specific period of development has lasting effects on the structure or function of organs, tissues and body systems. Some prefer to call these periods sensitive rather than critical if the insult is not completely deterministic.
- A critical period model with later effect modifiers
- An accumulation of risk model where insults are independent and uncorrelated
- An accumulation of risk model where insults are correlated either through clustering or as part of a biological and/or social pathway ("chains of risk").

Implication for overall study design: We propose that the NCS present itself from the start as a lifecourse study rather than specifically as a childhood health study. A major problem of some previous large US birth cohort studies was that they were presented as childhood follow-ups, providing a legitimate reason to discontinue the funding after the childhood period. As a result, in contrast to British birth cohort studies that were continued into adulthood, these US studies never realized their great potential as lifecourse investigations. This recommendation is particularly applicable to outcomes (eg, schizophrenia) some of which occur in the first 20 years of life but really become common enough to study thoroughly in the second 20 years.

Other general principles include the following:

1. Some good epidemiological evidence already exists on the early origins of adult disease. For example, it is established that lower birth weight is predictive of later cardiovascular disease and its risk factors. However, there are many remaining epidemiologic challenges, and there is a need to explore the biological mechanisms underlying the known associations.

2. Studying both genes and environment are important, in combination with each other. A particular reminder is that fetal environment is determined by maternal environment and the products of maternal genes. ("What is genetic for the mother is environmental for the fetus.")

Implication for overall study design: NCS would greatly benefit from genetically informative samples that could be built into the cohort. This would mean, in particular, making special efforts to recruit monozygotic twins and dizygotic twins. Information, including genetic data, on both mothers and fathers, will be critical. Inclusion of large numbers of same-sex sibling pairs would enhance the ability of the cohort to control for family level factors, and to some extent for genetic factors, when required. For some questions, tight control of these factors will be crucial for definitive findings.

3. Intriguing data from animal and human studies show that the prepregnancy period is important. In fact, intergenerational influences may help explain the etiology of some adult chronic diseases.

Implication for overall study design: Establishing a prepregnancy cohort would be extremely useful. This cohort could be much smaller than the overall NCS cohort, as many of the questions deal with how variables measured on a continuous scale change from prepregnancy to pregnancy. Short of a separate cohort, studying NCS cohort women between pregnancies will be helpful, but that approach will not include primigravidas.

4. Associations involving birth weight and fetal growth have dominated the recent epidemiologic literature. While it is critical to study patterns of prenatal and postnatal growth, it is also vital to go beyond growth measures to study not only their determinants, but other fetal influences on adult disease that are not "mediated" by birth weight or other growth measures.
5. Similarly, the concept of "low birth weight," well known to perinatal epidemiologists, is less useful in the early origins of adult disease. For example, most birthweight-adult disease associations in the literature span the birthweight spectrum, i.e., are not restricted to the lower end. Even high birth weight fetuses might be growth restricted relative to their genetic potential. In addition, higher birth weight is also associated with adverse outcomes, in particular obesity and type 2 diabetes.
6. Since the placenta is the conduit to the fetus for oxygen and nutrients, and is itself an active endocrine organ, it is likely to play a key role. Obtaining information on placental function and structure will be critical.
7. Socioeconomic factors are important, not only because they may confound relations of early life measures with adult outcomes, but because they may shed light on the actual early life etiologies under question. Getting "behind" SES to identify which factors play roles at different times of the lifecourse will be a conceptual and methodologic challenge worth pursuing.

Diversity of the study sample will be essential, as socioeconomic factors and race/ethnicity are already known or suspected to have effects on long-term disease outcomes in adults.

8. While it is attractive to limit hypotheses to modifiable exposures, it is also important to examine hypotheses that are currently only of biological interest. Today's seemingly arcane associations may lead to clinical or public health interventions decades from now.

Implication for overall study design from principles 4-8: To be maximally informative, NCS should collect data not only at many points along the lifecourse, but also that span a wide range of types of determinants, including but not limited to somatic growth patterns. It will be useful to select exposure measurements that provide a viable basis for longitudinal data analysis.

Specific Diseases

Working group members agreed that the diseases to be considered should be those that are serious and widespread, exerting a significant impact on U.S. public health. In addition, there should be a high probability that intermediate markers of these diseases can be measured during the first 20 years of life, since this is the proposed initial time period of the study. The group identified the following outcomes as fulfilling these criteria:

- Cardiovascular disease and risk factors, including hypertension and lipid disorders
- Diabetes
- Obesity
- End-stage renal disease
- Cancers (e.g., skin cancer, hormone-dependent cancers)
- Osteoporosis
- Addictive behaviors
- Reproductive health
- Neuropsychiatric outcomes

The group also identified several other potential outcomes, although each currently has one or more limitations:

- Alzheimer's disease and, more generally, cognitive decline
  Limitation: no clear intermediate marker in 1st 20 years
- Benign prostatic hyperplasia
  Limitation: unclear if markers exist in 1st 20 years
- Connective tissue diseases
  Limitation: outcome either occurs during 1st 20 years of life (making it no longer an "adult outcome") or no marker of later outcomes available; also frequency may be too low even in large cohort

Examples of intermediate markers of outcomes

1. Cardiovascular
    - Blood pressure
    - Blood levels of
        - Lipids
        - Inflammatory markers
        - Insulin resistance and secretion (using glucose and insulin)
    - Early markers of atherosclerosis
        - Endothelial function
        - Arterial distensability

2. Diabetes
    - Blood levels of glucose, insulin, glycosylated hemoglobin

3. Obesity
    - Height, weight, skinfolds, circumferences, DXA/CT/MRI measures of body composition

4. Renal disease
    - Microalbuminuria, creatinine clearance, ?direct functional studies

5. Cancers
    a. Skin—number of nevi, atypical nevi
    b. Hormonally-related cancers
        - Growth and anthropometry
        - Hormone levels, e.g., estrogens, androgens, prolactin, growth hormones (e.g., IGF's)

6. Osteoporosis
    - Bone mineral density

7. Addictive behaviors—measured in adolescence

8. Reproductive health
    - Age at menarche
    - Cycle length

9. Neuropsychatric outcomes
    - Incidence of schizophrenia

ILLUSTRATIVE HYPOTHESES

We attach below brief summaries of hypotheses that illustrate the principles of EOAH. We also attach a single Excel spreadsheet that proposes measurements applicable to the hypotheses. Since there is so much overlap of measurements among hypotheses, we elected to incorporate them all into a single spreadsheet rather than attach individual ones.

Titles of the attached hypotheses are

1. Maternal risk factors, placental compromise, and offspring cardiovascular risk

PROPOSED CORE HYPOTHESIS/QUESTION

- Cardiovascular risk is determined by placental compromise and subsequent glucorticoid activation, which programs offspring for elevated blood pressure and glucose intolerance/insulin resistance
- Placental compromise is associated with a constellation of maternal prenatal risk factors representing the "multiple metablolic (or insulin resistance) syndrome"
- Maternal prepregnancy and gestational diet are determinants of this syndrome

Public Health Significance:

- CHD and stroke are the #1 and #3 causes of death in the US. Hypertension affects 50 million Americans and is a major risk factor for CHD and stroke as well as other cardiovascular diseases and renal disease. Glucose intolerance and type 2 diabetes are rising in incidence, even in youth.

JUSTIFICATION FOR A LARGE, PROSPECTIVE, LONGITUDINAL STUDY

- Large— The childhood intermediate outcomes are generally continuous variables, appearing to require smaller sample sizes than projected. However, for blood pressure national organizations have recommended cutpoints that generally identify the extreme 5-15% of the population distribution, and frank diabetes is as important to detect as continuous measures of glucose intolerance or insulin resistance. In addition, even with continuous variables, examining effect modification (interaction among 2 or 3 variables, including gene x environment interactions) requires geometrically increased sample size.

- Prospective—needed for reliable information on many exposures of interest, eg, maternal diet during pregnancy, placental specimens, and infant and childhood anthropometry and blood specimens.

- Longitudinal— A lifecourse approach to adult health requires longitudinal data.

SCIENTIFIC MERIT

- Investigates pathways to explain observed epidemiologic associations of variation in birth weight with cardiovascular outcomes
- Could uncover new etiologic pathways
- Could lead to public health and/or clinical interventions among girls and women of reproductive age to prevent cardiovascular disease in the next generation

POTENTIAL FOR INNOVATIVE RESEARCH

- New paradigm for cardiovascular disease prevention
- Long-term effects of altered fetal environment
- Lifecourse approach to chronic disease
- New technologies
- Genetics/genomics/proteomics
- Maternal diet assessment
- Placental pathology
- Longitudinal data analysis
- Study intersection of biology and public health

FEASIBILITY/MEASUREMENTS—SEE SPREADSHEET

ETHICAL ISSUES

- When can parents enroll child?
- Is one parent enough?
- Is parental consent sufficient as well as necessary for all procedures?
- How often to consent
- Informing parents/children of individual results
- Divorce? Adoption?

2. Maternal glycemia and childhood adiposity/glucose tolerance

PROPOSED CORE HYPOTHESIS/QUESTION

- Impaired glucose tolerance (IGT) and/or gestational diabetes (GDM) causes, in childhood
    - Increased adiposity
    - Inreased risk of IGT/type 2 DM

Public Health Significance:

- Obesity is endemic in children and adolescents and rising rapidly over time
- Childhood/adolescent obesity is associated with multiple short- and long-term morbidities
- One of the most important is type 2 DM, whose prevalence is also apparently rising rapidly

JUSTIFICATION FOR A LARGE, PROSPECTIVE, LONGITUDINAL STUDY

- [Same as for Maternal risk factors, placental compromise, and offspring CVD risk]
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SCIENTIFIC MERIT

- GDM associated with higher birthweight and higher birthweight associated with obesity
- But previous studies show variable associations of DM in pregnancy and offspring obesity/IGT
    - Sample size
    - Endemic/severe DM v. mild (or treated) disease
    - Genetic inheritance
    - Timing of insult/delayed postnatal effect
    - Pre-existing DM v. GDM
- Studies needed to address each of these issues
- Also, need information about less severe glycemic states in pregnancy
- Need ways to stop vicious cycle of obesity → GDM → offspring obesity → …
- GDM prevention (and treatment?)

POTENTIAL FOR INNOVATIVE RESEARCH

- New paradigm for obesity/DM prevention

- Long-term effects of altered fetal environment
- Lifecourse approach to chronic disease
- Ability to investigate mechanisms
- New technologies
  - Genetics/genomics/proteomics
  - Longitudinal data analysis
- Study intersection of biology and public health

FEASIBILITY/MEASUREMENTS—SEE SPREADSHEET

3. Fetal growth retardation and subsequent catch-up growth are associated with higher blood pressure via telomeric shortening

PROPOSED CORE HYPOTHESIS/QUESTION

- Fetal growth retardation and subsequent catch-up growth are associated with higher blood pressure via telomeric shortening

Public Health Significance:

- Hypertension affects 50 million Americans and is a major risk factor for heart disease, stroke, and renal disease.
- New avenues for hypertension prevention are needed.

JUSTIFICATION FOR A LARGE, PROSPECTIVE, LONGITUDINAL STUDY

- [Same as for Maternal risk factors, placental compromise, and offspring CVD risk]
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SCIENTIFIC MERIT

- Epidemiologic studies show that hypertension is associated with the combination of lower birth weight and accelerated growth after birth
- Mechanisms are unkown
- Telomeres
- Non-coding DNA at ends of chromosomes
- Needed for cell replication
- At each mitosis, lose telomeric DNA
- “biological clocks” that mark cell senescence
- Telomere-driven senescence
    - By-product of tumor suppression system
    - Beneficial in early life but harmful in later life
    - Example of evolutionary trade off across the lifespan
- Kidney telomere length
- Reduced by
    - Oxidative and hemodynamic stress
    - Fetal growth retardation
    - Catch up growth

  Increased by
    - Postnatal growth retardation
- Thus telomere shortening uniquely associated with reduced prenatal and accelerated postnatal growth, the phenotype associated with increased risk of hypertension.

- Will require pilot studies for “prime time” exposure

POTENTIAL FOR INNOVATIVE RESEARCH

- New paradigm for hypertension prevention
- Lifecourse approach to chronic disease
- Ability to investigate mechanisms
- Unique hypothesis relating pre- and postnatal somatic growth to health outcome
- New technologies
  - Measuring telomeric shortening
  - Longitudinal data analysis
- Study intersection of biology and public health

Feasibility/Measurements—see spreadsheet

4. Fetal growth retardation is associated with higher blood pressure via congenital oligonephropathy

PROPOSED CORE HYPOTHESIS/QUESTION

- Pre-natal growth retardation permanently re-sets the number of nephrons in the kidney, impacting kidney size, function, and ultimately the later risk of hypertension (Brenner and Chertow, 1994).

Public Health Significance:

- Hypertension affects 50 million Americans and is a major risk factor for heart disease, stroke, and renal disease.
- New avenues for hypertension prevention are needed.

JUSTIFICATION FOR A LARGE, PROSPECTIVE, LONGITUDINAL STUDY

- [Same as for Maternal risk factors, placental compromise, and offspring CVD risk]
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SCIENTIFIC MERIT

- Epidemiologic studies show consistent inverse associations between birth weight and later blood pressure.
- Animal models--Maternal undernutrition reduces nephron number, kidney size, and fetal size, and increases risk of hypertension in offspring
- Human counterparts unknown
- Pilot work needed on accuracy of prenatal ultrasound and/or other measures

POTENTIAL FOR INNOVATIVE RESEARCH

- New paradigm for hypertension prevention
- Lifecourse approach to chronic disease
- Ability to investigate mechanisms
- Unique hypothesis relating prenatal organ growth to health outcome
- New technologies
  - Measuring proxy for nephron number prenatally
  - Longitudinal data analysis
- Study intersection of biology and public health

FEASIBILITY/MEASUREMENTS—SEE SPREADSHEET

5. Lifecourse Approach to Osteoporosis

PROPOSED CORE HYPOTHESIS/QUESTION

- Peak bone mass is an important determinant of osteoporotic fracture risk
- In addition to genetics, peak bone mass represents the cumulative effect of factors that affect growth, maturation, ovarian function, and bone mineralization
- Non-genetic determinants of bone mass:
  - Maternal diet and sun exposure during pregnancy
  - Diet - infancy, childhood and adolescence
  - Physical activity - infancy, childhood and adolescence
  - Health status - infancy, childhood and adolescence
  - Sun exposure - infancy, childhood and adolescence

Public Health Significance:

- High prevalence: One out of two women and one in eight men will have an osteoporotic fracture.
- High cost: nursing home and hospital costs total $13.8 billion each year.
- High mortality: 24% of hip fracture patients die within 1 year.
- Public recognition: growing

JUSTIFICATION FOR A LARGE, PROSPECTIVE, LONGITUDINAL STUDY

- There are no prospective studies of bone development that cover fetal life to early adulthood.

SCIENTIFIC MERIT

- Current knowledge from cross-sectional and short-term longitudinal studies
- Growth, maturation rate, lean mass, are strong correlates of bone mass
- Factors that affects the trajectory of growth may affect peak bone mass.
- Growth in early life influences peak bone mass - weight at one year of age is associated with adult bone mass and density.
- No data on whether compensations in growth rate (catch-up growth) result in compensations in bone mass accrual or whether early deficits in bone mass persist.
- Physical activity and dietary intake are correlates of bone mass in children and peak bone mass-- important questions about whether effects persist
- Child health and well-being are possible determinants of peak bone mass, e.g., chronic diseases, medications, and depression-- important questions about whether effects persist

POTENTIAL FOR INNOVATIVE RESEARCH

- The potential for innovative research is high.
- No longitudinal data on bone mass development from fetal life and infancy to attainment of peak bone mass exist
- long-term persistence of early deficits in bone mass is an important question

FEASIBILITY

- Critical period for exposures – fetal, infancy, childhood and adolescence
- Critical period for outcome – peak bone mass and density at age 20; data on bone mass at earlier ages will allow us to examine the effects of acute exposures and whether these effects persist
- Sample size needs – not large (n=200-2000) for common exposures, larger for rare exposures.
    - Ethics – Genotyping and radiation exposure

6. Early origins of skin cancers, including malignant melanoma, basal cell carcinoma and squamous cell carcinoma

Proposed General Hypothesis:

- Sun exposure during childhood and cumulative sun exposure are the major causes of malignant melanoma, basal cell and squamous cell cancers in susceptible populations.

    - Infant and childhood exposures to the sun without sufficient protection, with resulting sunburns are associated with adult skin cancers, including malignant melanoma, basal cell and squamous cell cancers
    - Cumulative lifetime exposure to the sun without sufficient protection is associated with increased risk of adult skin cancers
    - Dysplastic nevi, or abnormal moles, are precursor lesions for skin cancers, are associated with sun exposure and can be used as an intermediate end-point in adolescents and young adults.
    - Individuals of Northern European or United Kingdom origins are at increased risk of skin cancers. Those with fair skin, freckle easily and burn easily are at increased risk of skin cancers.
    - Family history of malignant melanoma is associated with risk factors for melanoma, including fair skin characteristics, number of nevi, and development of dysplastic nevi.

Public Health Significance:

- In 2002, more than 1 million highly curable cases of basal cell or squamous cell carcinomas will be diagnosed in the United States
- The more serious form of skin cancer, malignant melanoma, will be diagnosed in approximately 30,100 males and 23,500 females
- Although malignant melanoma is a relatively rare tumor, incidence rates are increasing worldwide and in the United States by about 3% per year
- The overall 5-year survival rate for malignant melanoma is 89%, however, it is 61% and 12% for individuals with regional or distant spread of the cancer
- Physical, psychological and financial toll for the surgical removal of millions of moles is of public health concern
- New research documenting the etiologic links and specifying the susceptibility factors will help target future public health messages

Justification for a large, prospective, longitudinal study:

- There have been no long-term studies of sun exposure and sun protection from birth through adulthood.
- There is potential for longer follow-up of the cohort to a cancer outcome, or to development of dysplastic nevi, which are precursor lesions for skin cancers that begin to appear around puberty.

Scientific Merit

- The major risk factor for all skin cancers is excessive sun exposure, especially in susceptible populations and exposure at young ages
- Risk factors specifically for malignant melanoma include UV radiation, melanocytic nevi (moles), fair hair color, light eye color, increased freckling, and an inability to tan
- Studies of individuals migrating to areas of high sun exposure indicate that age at migration is a more important variable than duration in the new country, migration at ages less than 10 may be critical
- Sun exposure patterns seem to be important, with higher risk for intermittent sun exposure than total lifetime exposure
- Studies to date have relied on recall of the distant past and have been unable to accurately document any influence of perinatal and early childhood exposures
- Sun exposure is related to increased risk of malignant melanoma in susceptible individuals but it is not a simple relationship and inconsistencies have yet to be explained
- There are likely to be gene-environment interactions that could be evaluated in a large, population-based study, which have not been attempted in children
- Understanding melanoma has public health importance for this cohort and future cohorts due to the increasing exposure to UV radiation

VII. Potential for innovative research

- Given the lack of documented early sun exposure, there is clear need for longitudinal data on time periods of vulnerability for this cancer
- There may be gene-gene and gene-environment interactions as well as a need for evaluating risk factor interactions

- There is potential for identification of novel risk factors, as well as investigating new hypotheses that will emerge in the coming decade

Feasibility

- Critical time periods for exposure – fetal, infancy, childhood and adolescence
- Critical time periods for outcome – dysplastic nevi may appear in adolescence, but malignant melanoma is unlikely to have sufficient incidence in this cohort, and could only be assessed in a larger sample than 100,000 males and females, and with longer follow-up

Ethical considerations:

- The influence of collecting DNA for later evaluation presents ethical questions and is hopefully being addressed by the gene-environment working group.
- Subjects, especially those with risk factors, would receive usual medical recommendations to minimize UV exposure and to use sunscreen. There are no additional recommendations for subjects with genetic susceptibility.

7. Early origins of hormone-responsive adult cancers

Proposed Core Hypotheses

- In utero and childhood environment and growth affects risk of adult cancers. The principal cancers of interest include those of the breast, prostate, and testes.
    - In utero environment, defined as hormone concentrations, integrity of the placenta, exogenous exposures from dietary intake of nutrients and other dietary constituents can affect risk of adult breast, prostate and testicular cancers.
    - Growth in utero, birth weight, birth length, ponderal index, head circumference, measures of digit lengths reflect in utero exposures and may be related to risk of a variety of cancers.
    - Postnatal and childhood growth patterns may be related to puberty and may be related to a variety of cancers.
    - Diet during pregnancy, in the first year, and diet composition and energy intake or energy balance in childhood may be related to growth velocity and to risk of a variety of cancers.
    - Childhood, adolescent and age 18 body mass index may be related to risk of adult breast cancers.
- Greater stature is associated with a variety of cancers including breast, prostate, colorectal and hematopoietic cancers.

Public Health Significance:

- Breast and prostate cancers are the leading cancers in women and men, respectively, in the U.S. with approximately 200,000 new cases each year.
- Testicular cancer appears in young man beginning at puberty with a peak incidence age 25-30
- Increasing incidence of testicular cancer, with an estimated 7,500 new cases this year
- Evidence suggests strong link of testicular cancer to in utero environment
- The estimated costs for all cancer diagnoses and treatments are approximately $157 billion in the U.S.
- Great public interest in cancer research and prevention

Justification for a large, prospective, longitudinal study

- Most of the evidence has been derived from record linkage studies in Scandinavian countries where national identification numbers are linked between cancer registry data and birth data

- The principal limitation in all of the previous studies has been the use of available data as opposed to hypothesis-driven data collection
- No large prospective studies that cover fetal life to adulthood

Scientific Merit

- Current knowledge from record linkage, case-control and small cohort studies – all designs with methodologic limitations
- Early life risk factors for breast, prostate and testicular include the following;
    - High birth weight, high birth weight for gestational age (breast and prostate cancers)
    - Low birth weight and small for gestational age (testicular cancer)
    - Preeclamptic pregnancy (reduced risk)
    - Prematurity
    - Jaundice
    - Maternal AFP
    - Maternal Insulin-like Growth Factors (IGFs)
    - Growth velocity in utero and in childhood
    - Attained height
- A large proportion of the attributable risk for breast, prostate and other cancers have yet to be identified
- Integration of risk factors identified throughout the life course and evaluation of relations among risk factors could advance our understanding of cancer etiology and prevention

Potential for innovative research

- Research into the early origins of adult cancers is a relatively new area and has been investigated in the past 10-12 years and only for some cancers
- New research approaches have been recommended for studying the etiology of breast and other cancers
- The area of early life factors holds tremendous promise as setting the stage for effects of other risk factors identified in adulthood
- With this comprehensive study, risk factors and biologic mechanisms for risk factors can be evaluated over time, within an individual
- Using intermediate outcomes, and potentially early onset cancers if the study were extended, this study provides the optimal format for the life course approach to cancer epidemiology

Feasibility

- Critical time periods for exposure – fetal, infancy, childhood and adolescence
- Critical time periods for outcome – testicular cancer may appear in adulthood but is unlikely to have sufficient incidence in this cohort, and other cancers could only be assessed in a larger sample than 100,000 males and females, and with longer follow-up
- Intermediate markers can be assessed in sub-sample of the group. Evaluation among risk factors can also be addressed in subgroups (1000-2000).

Ethical considerations:

- Any abnormalities identified in the blood collection or in anthropometric measurements would be noted and appropriate follow-up medical care would be recommended.
- The influence of collecting DNA for later evaluation presents ethical questions and is hopefully being addressed by the gene-environment working group.

7. PRENATAL EXPOSURES AND SCHIZOPHRENIA

Hypothesis/Question

It is now widely accepted that many cases of schizophrenia are neurodevelopmental in origin, and that both genes and environment play a role in the etiology of these cases. Several prenatal exposures have been linked to risk of offspring schizophrenia, including nutritional deficiencies, infections, toxic exposures, maternal body-mass index, and traumatic exposures. We propose that maternal neuroendocrine changes – disturbance in the maternal HPA axis – mediate the effect of a variety of prenatal insults on schizophrenia risk. The effects of these maternal changes are in turn mediated by uteroplacental insult that impacts directly on the fetus. This hypothesis is in accord with a unifying theme of some other proposals from this working group, which also focus on the HPA axis.

Public Health Significance:

Schizophrenia is a severe psychiatric disease typically appearing in late adolescence or early adulthood. The prevalence of the disorder is approximately 1% in the general population. It is associated with significant long-term morbidity, occupational disability, social disadvantage, and high mortality from suicide and other causes.

Justification

To advance investigations of the prenatal origins of schizophrenia requires very large prospective cohorts. The disease is relatively rare. In addition, biological specimens are required for precise prenatal exposure data. We have previously shown that this method can illuminate schizophrenia etiology, albeit in smaller studies which were therefore not conclusive. As described above, it is an illness which contributes a great deal to chronic mental morbidity and has a large social impact as well as economic consequences. Thus, such an investigation is needed, feasible, and societally apt.

VI. Scientific merit

Despite intriguing results from previous studies, which associate prenatal exposures with schizophrenia risk (see above), results are not yet not conclusive for any prenatal exposure. To advance this research, we need precise exposure data – including biological specimens - in large and well defined cohorts. We have argued this point extensively elsewhere. The biological specimens needed include serologic samples, ultrasound images of the brain in fetal and infant life, and placental specimens.

Although several hypotheses could and should be tested using the biological and other exposure data collected, we will limit this brief note to one hypothesis that has been put forth by many investigators in this field. We propose (also see above) that maternal

neuroendocrine changes – disturbance in the maternal HPA axis – mediate the effect of a variety of prenatal insults on schizophrenia risk. The effects of these maternal changes are in turn mediated by uteroplacental insult that impacts directly on the fetus.

It is our assumption that the needed questionnaire data, serologic samples and ultrasound brain images that are already planned will be sufficient for use in schizophrenia studies. Due to space limitations, we will not detail them here. Rather, we will focus on the use of placental data, which are not often collected in a routine and reliable and comprehensive fashion, and therefore, may need to be given special attention.

Placental data can be used to indicate nutritional, infectious, toxic, and other exposures, and can also be used to indicate HPA disturbance. The potential role of placental data for investigations of fetal neurodevelopment has been long appreciated. Fetal stresses that potentially disrupt neurodevelopment may work by altering the fetal circulatory, nutrient, oxygen and/or cytokine milieu. These changes may either be directly caused by placental damage, or may be secondarily reflected in placental damage. The central contribution of placental pathology is to provide a window on fetal life and environment, and a closer look at prenatal pathological processes. In previous birth cohort studies, however, the reliability and validity of placental measurements was not well established. We can now do far better (see below).

VII. Potential for innovative research

Relating placental indicators of HPA abnormalities to schizophrenia would be highly innovative. It represents the cutting edge of current thinking about brain disorders, as well as some other health domains, and also would be unprecedented.

VIII. Feasibility

To keep this brief, we address here the nature of placental measurement in a somewhat general way. Specific indicators of HPA abnormalities in placental data and other aspects of feasibility will be included if the hypothesis is approved for further consideration at our informal working group meeting.

Gross Placental Measurement: The gross placenta can be described by many individual – but not independent- measurements that, together and in combination, can inform on the cumulative effects of the intrauterine environment on the conceptus, and can contribute to timing their onset back to as early as the last weeks of the first trimester (Boyd and Hamilton, 1970).

Novel technologies of digital image capture allow new measurement goals of improved reliability of measure previously done by hand with a tape measure, as well as capture of subtle deviations in growth. Irregular shape of the disk has been long recognized as a potential marker of fetal stress. Such placentas will not have their disk growth captured in measurement of a single length and width, the standard placental measures; similarly only the exceptional and uncomplicated normal term placenta will have its thickness captured by a single cm. measurement. Image capture and image analysis can improve reliability of standard gross measures, extend the range of what can be measured in the gross placenta, and can simplify the gross examination of the placenta. Digital image capture can be performed more simply than completing a complex gross examination protocol. The archived images can be transferred to a central site for analysis.

Histology Measurement: . Some important evidence regarding conceptus (and potentially fetal) exposures that can only be collected through histology review. The development of a reliable and validated histology scoring instrument is well under way and the instrument will be avaialable for use in the new cohort.

Histologic data are especially useful for indicating three distinct types of intrauterine pathophysiology: vascular pathology, and acute or chronic inflammation. Vascular pathologies impair placental functions of nutrient and oxygen transfer, and affect fetal cardiovascular homeostasis. Intrauterine inflammation represents a fetal-placental environment characterized by abnormal exposure to products of activated maternal and fetal immune systems that potentially alter placental growth, function and fetal integrity. The distinction between acute and chronic inflammation lies in the different agents (acute- bacterial, chronic- viral) and route of fetal exposure (acute- intraamniotic, chronic-hematogenous).